Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity and chronic toxicity studies have been conducted in laboratory rats and dogs. No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving daily oral doses up to 60 mg/kg of Ludiomil for eighteen months or in dogs receiving daily oral doses up to 30 mg/kg of Ludiomil for one year. In addition, no evidence of mutagenic activity was found in offspring of female mice mated with males treated with up to 60 times the maximum daily human dose.

Pregnancy Category B: Reproduction studies have been performed in female laboratory rabbits, mice, and rats at doses up to 1.3, 7, and 9 times the maximum daily human dose respectively and have revealed no evidence of impaired fertility or harm to the fetus due to Ludiomil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Although the effect of Ludiomil on labor and delivery is unknown, caution should be exercised as with any drug with CNS depressant action.

Nursing Mothers: Ludiomil is excreted in breast milk. At steady state, the concentrations in milk correspond closely to the concentrations in whole blood. Caution should be exercised when Ludiomil is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

The following adverse reactions have been noted with Ludiomil and are generally similar to those observed with tricyclic antidepressants.

Cardiovascular: Rare occurrences of hypotension, hypertension, tachycardia, palpitation, arrhythmia, heart block, and syncope have been reported with Ludiomil.

Psychiatric: Nervousness (6%), anxiety (3%), insomnia (2%), and agitation (2%); rarely, confusional states (especially in the elderly), hallucinations, disorientation, delusions, restlessness, nightmares, hypomania, mania, exacerbation of psychosis, decrease in memory, and feelings of unreality.

Neurological: Drowsiness (16%), dizziness (8%), tremor (3%), and, rarely, numbness, tingling, motor hyperactivity, akathisia, seizures, EEG alterations, tinnitus, extrapyramidal symptoms, ataxia, and dysarthria.

Anticholinergic: Dry mouth (22%), constipation (6%), and blurred vision (4%); rarely, accommodation disturbances, mydriasis, urinary retention, and delayed micturition.

Allergic: Rare instances of skin rash, petechiae, itching, photosensitization, edema, and drug fever.

Gastrointestinal: Nausea (2%) and, rarely, vomiting, epigastric distress, diarrhea, bitter taste, abdominal cramps and dysphagia.

Endocrine: Rare instances of increased or decreased libido, impotence, and elevation or depression of blood sugar levels.

Other: Weakness and fatigue (4%) and headache (4%); rarely, altered liver function, jaundice, weight loss or gain, excessive perspiration, flushing, urinary frequency, increased salivation, and nasal congestion.

Note: Although the following adverse reactions have not been reported with Ludiomil, its pharmacologic similarity to tricyclic antidepressants requires that each reaction be considered when administering Ludiomil.

—Bone marrow depression, including agranulocytosis, eosinophilia, purpura, and thrombocytopenia, myocardial infarction, stroke, peripheral neuropathy, sublingual adenitis, black tongue, stomatitis, paralytic ileus, gynecomastia in the male, breast enlargement and galactorrhea in the female, and testicular swelling.

OVERDOSAGE

Animal Oral LD_{50}: The oral LD_{50} of Ludiomil is 600-750 mg/kg in mice, 760-900 mg/kg in rats, > 1000 mg/kg in rabbits, > 300 mg/kg in cats, and > 30 mg/kg in dogs.

Signs and Symptoms: Data dealing with overdosage in humans are limited with only a few cases on record. Symptoms are drowsiness, tachycardia, ataxia, vomiting, cyanosis, hypotension, shock, restlessness, agitation, hyperpyrexia, muscle rigidity, athetoid movements, mydriasis, cardiac arrhythmias, impaired cardiac conduction. In severe cases, loss of consciousness and generalized convulsions may occur. Since congestive heart failure has been seen with overdosages of tricyclic antidepressants, it should be considered with Ludiomil overdosage.

Treatment: There is no specific antidote. Induced emesis and gastric lavage are recommended. It may be helpful to leave the tube in the stomach with irrigation and continual aspiration of stomach contents possibly promoting more rapid elimination of the drug from the body. The room should be darkened, allowing only minimal external stimulation to reduce the tendency to convulsions.

1. The intravenous administration of 1 to 3 mg of physostigmine has been reported to reverse the signs and symptoms of overdosage with tricyclic antidepressants. Repeat doses at intervals of 30 to 60 minutes may be necessary.
2. Hyperirritability and convulsions may be treated with carefully titrated parenteral barbiturates. Barbiturates should not be employed, however, if drugs that inhibit monoamine oxidase have also been taken by the patient in overdosage or in recent therapy. Similarly, barbiturates may induce respiratory depression, particularly in children. It is therefore advisable to have equipment available for artificial ventilation and resuscitation when barbiturates are employed. Paraldehyde may be used effectively in some children to counteract muscular hypertonus and convulsions with less likelihood of causing respiratory depression.
3. Shock (circulatory collapse) should be treated with supportive measures such as intravenous fluids, oxygen, and corticosteroids.
4. Hyperpyrexia should be controlled by whatever means available, including ice packs if necessary.
5. Signs of congestive heart failure may be satisfactorily treated by rapid digitalization.
6. Dialysis is of little value because of the low plasma concentration of this drug.

DOSAGE AND ADMINISTRATION

A single daily dose is an alternative to divided daily doses. Therapeutic effects are sometimes seen within 3 to 7 days, although as long as 2 to 3 weeks are usually necessary.

Initial Adult Dosage: An initial dosage of 75 mg daily is suggested for outpatients with mild-to-moderate depression. However, in some patients, particularly the elderly, an initial dosage of 25 mg daily may be used. Because of the long half-life of Ludiomil, the initial dosage should be maintained for two weeks. The dosage may then be increased gradually in 25-mg increments as required and tolerated. In most outpatients a maximum dose of 150 mg daily will result in therapeutic efficacy. It is recommended that this dose not be exceeded except in the most severely depressed patients. In such patients, dosage may be gradually increased to a maximum of 225 mg.

More severely depressed, hospitalized patients should be given an initial daily dose of 100 mg to 150 mg which may be gradually increased as required and tolerated. Most hospitalized patients with moderate-to-severe depression respond to a daily dose of 150 mg although dosages as high as 225 mg may be required in some cases. Daily dosage of 225 mg should not be exceeded.

Elderly Patients: In general, lower dosages are recommended for patients over 60 years of age. Dosages of 50 mg to 75 mg daily are usually satisfactory as maintenance therapy for elderly patients who do not tolerate higher amounts.

Maintenance: Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Dosage may be reduced to levels of 75 mg to 150 mg daily during such periods, with subsequent adjustment depending on therapeutic response.

HOW SUPPLIED

Tablets 25 mg — oval, dark orange, coated (imprinted CIBA 110)
Bottle of 100 — NDC 0083-0110-30
Accu-Pak® Unit Dose (blister pack)
Box of 100 (strips of 10) — NDC 0083-0110-32

Tablets 50 mg — round, dark orange, coated (imprinted CIBA 26)
Bottle of 100 — NDC 0083-0026-30
Accu-Pak® Unit Dose (blister pack)
Box of 100 (strips of 10) — NDC 0083-0026-32

Tablets 75 mg — oval, white, coated (imprinted 135 CIBA)
Bottle of 100 — NDC 0083-0135-30
Accu-Pak® Unit Dose (blister pack)
Box of 100 (strips of 10) — NDC 0083-0135-32

Dispense in tight container (USP).

Printed in U.S.A. C83-22 (Rev. 7/83)

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA

Watson

You are cordially invited–

CIBA has commissioned prominent artists to create their own interpretation of the elderly in a series entitled, "Portraits of Aging." Just as Toulouse-Lautrec's portrait of his mother is a classic, we believe these works by new masters have the potential to become classics with time.

I hope you are enjoying the first painting in this series, "Old Man with Guitar," by Luis Arvelo. The second painting is "Janet in the Rose Garden," by Postimpressionist Peter Fiore. A limited number of prints will be made from the original, available exclusively to physicians who respond to this invitation. When the offer is fully subscribed, the plates will be destroyed and no additional prints will ever be made. To reserve a free, limited edition print, please fill in the R.S.V.P. card attached to this invitation. When the R.S.V.P. card attached to this invitation and do not enjoy life as "Janet in the Rose Garden" so obviously does. Treatment with Ludiomil is a good choice for these patients because age makes them particularly vulnerable to side effects. Ludiomil rarely causes cardiovascular or severe anticholinergic side effects.

Older depressed patients often complain of sleep disturbances. The antidepressant/antianxiety effect of Ludiomil helps them get a good night's sleep. Seizures have been reported with Ludiomil at a rate of less than 1/10 of 1%. This risk may be reduced by: Initiating therapy at 75 mg (25 mg in the elderly)... Maintaining the initial dosage for two weeks (because of Ludiomil's long half-life)... If necessary, increasing dosage by 25-mg increments gradually. Do not exceed 150 mg daily except in severely depressed patients. Maximum dosage should not exceed 225 mg daily. In most patients, a maximum dosage of 150 mg daily will result in therapeutic efficacy. See Prescribing Information for details.

Cordially,

Audrey G. Kriegman, M.D.

Audrey G. Kriegman, M.D.
Director, Medical Services

P.S. To receive your complimentary limited edition print of Peter Fiore's "Janet in the Rose Garden," please fill in the attached R.S.V.P. card.

Ludiomil®
maprotiline HCl

for the eld